Proteinuria

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Faculty/Presenter Disclosure

- **Faculty:** Andrea Mazurat

- **Relationships with commercial interests:**

  None

Objectives

- Define proteinuria
- Methods of measuring proteinuria
- Causes of proteinuria
- Identify clinical situations where proteinuria may be identified and the differential diagnosis
- Treatment of proteinuria

Definitions

Proteinuria is the presence of protein in the urine

- Mostly albumin vs other proteins (light chains)

Normal urinary protein excretion is <150 mg in 24 hours

- 50 mg of filtered plasma protein
- 100 mg of secreted tubular proteins (Tamm-Horsfall mucoprotein)

Definitions

Persistent albumin excretion between **30-300 mg/day** is called moderately increased albuminuria (formerly "microalbuminuria")

Albumin excretion **>300 mg/day** is overt proteinuria/severely increased albuminuria (formerly "macroalbuminuria")

>2000-3000 mg/day is "glomerular range" proteinuria

Measurement of proteinuria

Dipstick analysis provides a semiquantitative measurement

- Primarily detects albumin

False positive results can occur with:

- Alkaline urine (pH >8)
- If dipstick is immersed too long
- Highly concentrated urine
- Gross hematuria
- Pus, semen, vaginal secretions

Need to confirm with a quantitative method

Quantitative measurement

Gold standard remains the 24 hour collection

- Cumbersome
- Over- or under-collection common
- Specific instructions required

Spot urine collections have been developed

- Urine albumin:creatinine ratio (UACR)
- Urine protein:creatinine ratio (UPCR)

Conversion of spot urine to 24 hour urine collection

Proteinuria Conversion Table

ACR (mg/mmol)	24 hr proteinuria(g)
≤ 3.5	< 0.15
3.6 – 29	0.15 – 0.499
30 – 69	0.5 – 0.99
70 – 150	1.0 – 1.5
151 – 450	1.5 – 4.5
> 450	> 4.5

Modified and Adapted from Lamb E, Mackenzie F, et al., Annals of Clinical Biochemistry 2009; 46: 205- 217

https://www.kidneyhealth.ca/health-care-providers/referral-pathway/proteinuria-conversion-table/

Proteinuria measurement

Estimating 24-hour protein excretion using a spot collection:

Multiply UACR or UPCR by 10

UACR: 100 mg/mmol x 10 = 1000 mg/day or 1 gram/day

UACR: 200 mg/mmol x 10 = 2000 mg/day or 2 grams/day

This is an estimation using the expected 24-hour urine creatinine excretion based on a 70 kg person

- 24-hour urine creatinine excretion expected to be 0.15 mmol/kg ± 0.03 mmol/kg

Spot urine collection limitations

Limitations of spot urine collection:

- Protein excretion varies throughout the day, lowest first thing in the morning
- Creatinine excretion increases in more muscular people, decreases in less muscular people leading to over- or under-estimation

Factors which will increase proteinuria temporarily:

- Fever
- Intense exercise
- Dehydration

UACR vs UPCR

UACR used for screening in patients with diabetes

UPCR used for glomerulonephritis

The two tests should give relatively similar results in most clinical scenarios

- Notable exception is multiple myeloma where the protein is non-albumin free light chains
- In this setting UPCR is much higher than UACR

Do you need to do 24-hour urine collection?

Usually not

UACR and UPCR are sufficient to make the diagnosis

- Make sure to repeat the test
- Trend and magnitude of proteinuria more important than the absolute number

24-hour urine collection useful in making treatment decisions in Nephrology clinic

Types of proteinuria

Glomerular

Tubular

Overflow

The Nephron

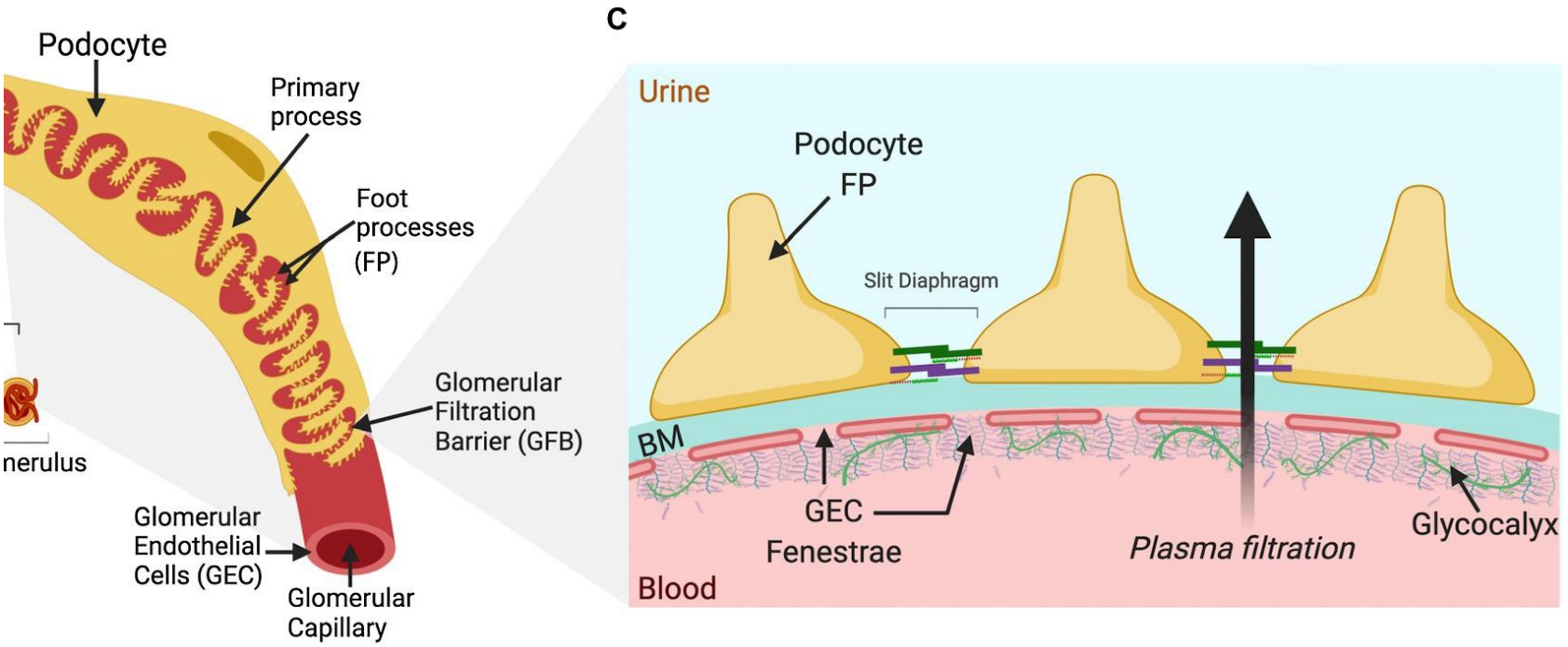
Glomerular proteinuria

Proteinuria associated with diabetic nephropathy and other glomerular diseases

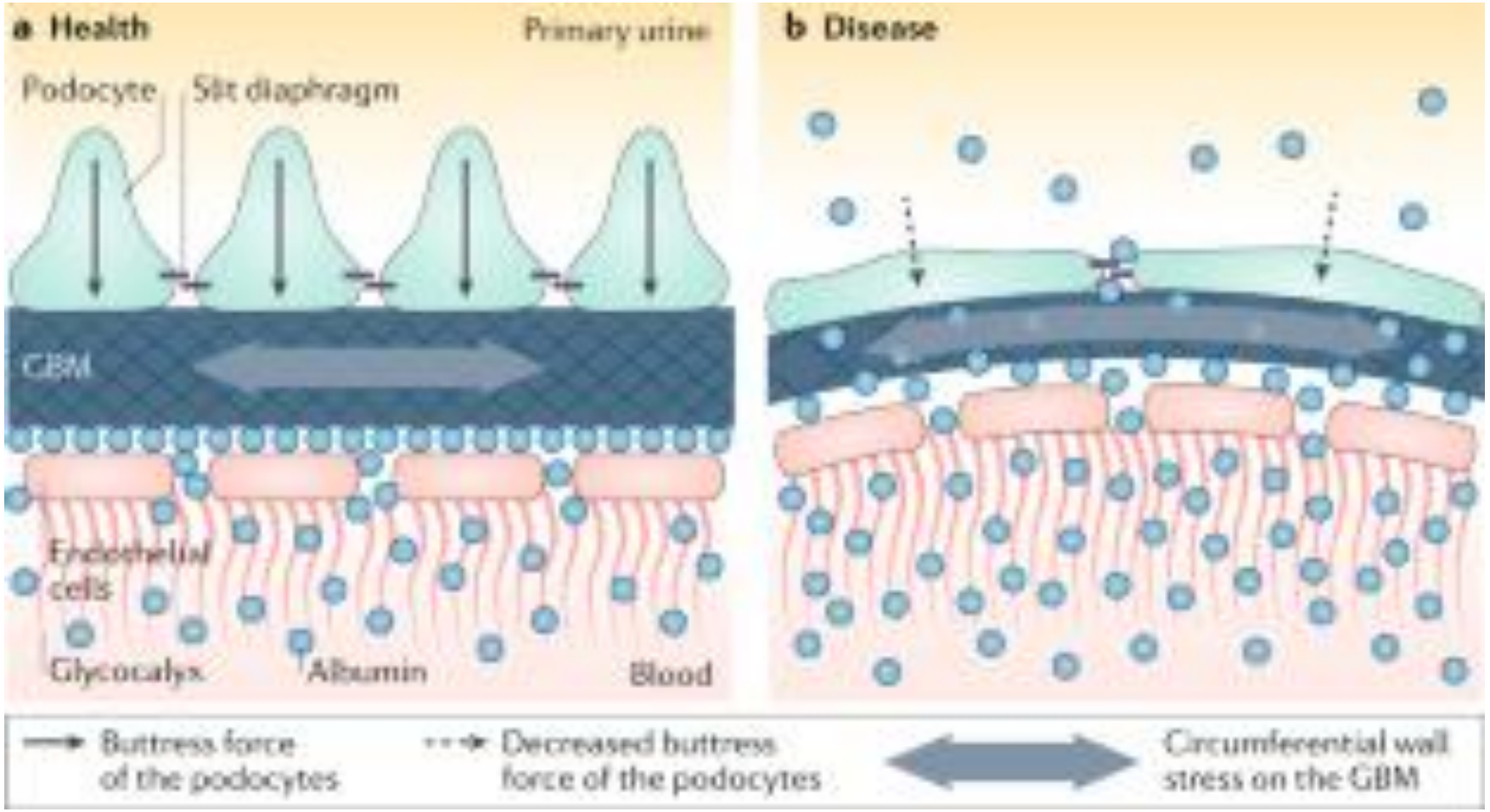
Can represent any amount of proteinuria, but the higher the protein excretion the more likely that it's glomerular in origin

- >2-3 grams per day is assumed to be glomerular in origin

Glomerular proteinuria



Ebefors, K et al. Front. Physiol., 02 June 2021. https://doi.org/10.3389/fphys.2021.689083



Moeller, M.J., Chia-Gil, A. A step forward in understanding glomerular filtration. *Nat Rev Nephrol* **16,** 431–432 (2020)

Tubular proteinuria

Low molecular weight proteins can be filtered across the glomerulus

- They are almost completely reabsorbed in the proximal tubule

Tubulointerstitial disease can interfere with proximal tubular reabsorption and result in increased excretion of these smaller proteins

- Ex: Hypertensive nephrosclerosis

Classically causes <2 grams per day of proteinuria

Tubular proteinuria

Overflow proteinuria

Low molecular weight proteins overwhelm the ability of the proximal tubule to reabsorb filtered proteins

Classically associated with multiple myeloma

Light chains are non-albumin proteins and therefore won't be picked up on a dipstick

- Need to do a protein-creatinine ratio or urine electrophoresis as well as a serum free light chain ratio

Overflow proteinuria

How does proteinuria present?

Symptomatic: in the setting of glomerulonephritis with nephrotic syndrome or other systemic complaints

Asymptomatic:

- Discovered in the setting of abnormal kidney function or hematuria
- Discovered in the setting of normal kidney function
  - Screening for diabetic nephropathy
  - Associated conditions – lupus
  - Screening test done for other reasons – insurance physical

Why do we care about proteinuria?

Need to identify those conditions that are imminently life- or kidney-threatening vs those that require less urgent diagnosis and management

Life- or kidney-threatening

Rapidly progressive glomerulonephritis

- ANCA vasculitis, anti-GBM disease, lupus nephritis, aggressive variant of any other GN

Multiple myeloma

Glomerulonephritis causing severe nephrotic syndrome

- Thromboembolic events are a known complication of nephrotic syndrome

Why do we care about proteinuria?

The more proteinuric a patient is, the more likely they are to have progressive CKD

Treatment of the proteinuria is a ***modifiable*** risk factor

Example using the Kidney Failure Risk Equation:

65 year old male with eGFR of 45 mL/min and UACR 3 mg/mmol:

Risk of ESRD at 2 years is **0.51%** and **1.58%** at 5 years

Same example, UACR 30 mg/mmol:

2 year risk **1.43%** and **4.4%** at 5 years

UACR 300 mg/mmol:

2 year risk **3.99%** and **11.93%** at 5 years

Presenting complaints with nephrotic syndrome

Acute onset edema

- May be accompanied by periorbital edema, ascites

Weight gain

- Can be upwards of 20-50 lbs of fluid

Fatigue/malaise

Other systemic symptoms depending on the underlying disease

Questions to ask on history

Past Medical History

- Lupus, diabetes, multiple myeloma, previous episodes of nephrotic syndrome

Onset and duration of edema

Weight gain

Associated symptoms:

- **Red flags**: Systemic symptoms (fevers/chills), hemoptysis, significant ENT symptoms (epistaxis, new hearing issues), rash, new joint abnormalities, “tea” or “cola” coloured urine, fevers/chills, back pain

Questions to ask on history

New/change in medications:

- NSAIDS, bisphosphonates,
- Recently discontinued ACE-I/ARB or diuretics

Exposures:

- Cocaine, heroine, anabolic steroids

Recent infections

- Strep throat
- Skin infections

Physical exam

Weight

Blood pressure

Respiratory exam

CV exam (looking for other causes of edema)

Abdominal exam (ascites)

Rheumatologic exam: Rashes, active joints

Extremity exam: Wounds, peripheral edema

Initial investigations

Bloodwork:

Electrolytes

Urea/creatinine

Albumin

HgA1c

Urine:

Urinalysis

Urine ACR

Urine PCR

Investigations

Bloodwork:

Electrolytes: Usually normal

Urea/creatinine: Creatinine may be elevated compared to baseline (or may be at baseline)

Albumin: Often lower than usual (can be <20 g/L)

HgA1C: ?Diabetes

Urine:

Urinalysis: >3 g/L protein, +/- RBC and RBC casts

Urine ACR: >200 mg/mmol

Urine PCR: >200 mg/mmol

Different types of glomerulonephritis

I've included the tables, but this is WAY too much information to review

I've highlighted the conditions that usually cause sudden-onset edema/nephrotic syndrome without other obvious abnormalities on investigations and history/physical

I've included a slide of what I call the "Nephro Stamp" – if you order all those investigations, you have ordered almost everything to rule-in or out a specific etiology

GN	Secondary causes	Investigations
Membranous	Lupus Malignancy Drugs (NSAIDs) Hepatitis B Syphylis	ANA, dsDNA Hepatitis B serology
Minimal change disease	Lymphoma Drugs (NSAIDs, lithium)	
Focal Segmental Glomerulosclerosis (FSGS)	Drugs (heroin, pamidronate) HIV Scarring: chronic reflux, obesity	HIV serology
Paraprotein (amyloid)	Multiple myeloma Amyloid	SPEP Free light chain ratio
Diabetes		HgA1c

Non-proliferative/nephrotic GNs
Classically cause nephrotic syndrome in association with heavy proteinuria

Bernstein, Keevin. Nephrology Notes: A Made-in-Manitoba Undergraduate Resource

GN	Secondary causes	Investigations
ANCA	Vasculitis	ANCA
Anti-GBM	Vasculitis	Anti-GBM
IgA nephropathy		
Infection-related	Any infection Classically after strep throat	ASOT Usually low C3
Lupus		ANA, dsDNA C3 and C4 may be low
Membrano-proliferative GN	Hepatitis C	Hepatitis C

Proliferative/nephritic GNs Don't classically cause nephrotic syndrome. Associated with less pronounced proteinuria and hematuria

Bernstein, Keevin. Nephrology Notes: A Made-in-Manitoba Undergraduate Resource

Initial investigations summary: “Nephro Stamp”

HgA1c

Viral serology: Hepatitis B, C, HIV

Autoimmune serology: ANA, dsDNA, C3, C4, ANCA, anti-GBM

SPEP, Free light chain ratio

Renal ultrasound

Urinalysis

Urine ACR/PRC

+/- ASOT (anti-streptolysin O titer)

When to consult nephrology

Anytime there is consistent proteinuria with UACR >100 mg/mmol

Triaged as urgent if:

UACR >200 mg/mmol and signs of nephrotic syndrome (please describe in the consult)

Call Nephrology if:

- Red flags on history
- Rapidly worsening creatinine
- Severe nephrotic syndrome

Manitoba renal program referral pathway

https://www.kidneyhealth.ca/health-care-providers/referral-pathway/referral-pathway-tool/

MRP Kidney Disease Referral Pathway Tool

eGFR < 15 ACR <100mg/m... Hematuria Yes

eGFR = estimated Glomerular Filtration Rate ACR = Albumin Creatinine Ratio

Next Steps

DOWNLOAD DIABETIC NEPHROPATHY MANAGEMENT GUIDELINES

DOWNLOAD NON-DIABETIC CKD MANAGEMENT GUIDELINES

Proteinuria in the context of diabetic kidney disease

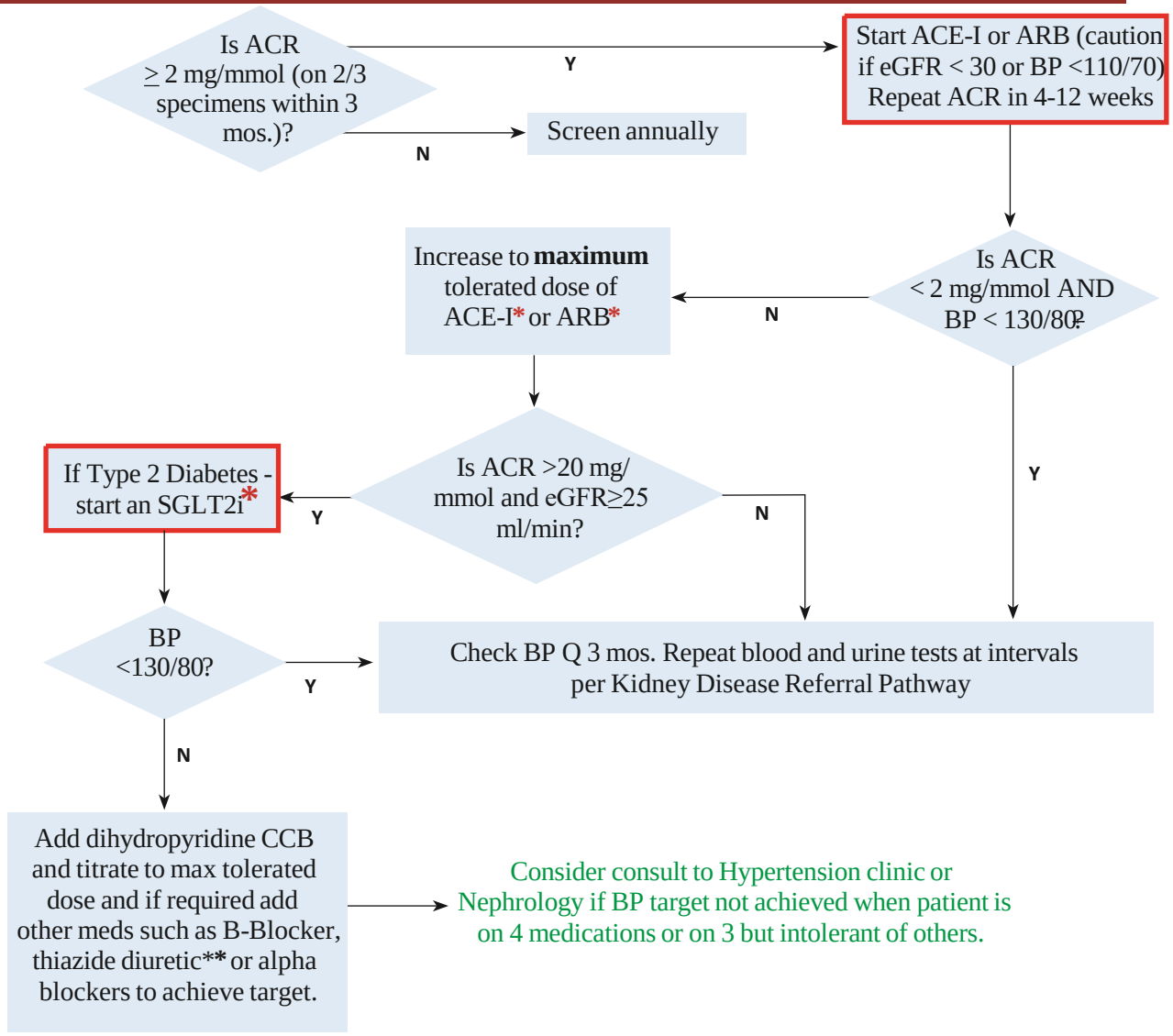
Patients with diabetes can develop other causes of kidney disease

- Consider if the severity of diabetes doesn't correlate with the severity of the kidney disease

Manitoba Renal Program

kidneyhealth.ca manitoba renal program

Diabetic Nephropathy Management Guidelines



SGLT-2 inhibitors (SGLT2-i)

Can continue SGLT2-i until dialysis or transplant

Empagliflozin 10 mg po daily (EMPA Kidney)

Canagliflozin 100 mg po daily (CREDENCE)

Dapagliflozin 10 mg po daily (DAPA-CKD)

Check creatinine 1-3 weeks after starting SGLT2i

- Expect up to a 25% increase in Cr
- If there is an increase in Cr >25% repeat Cr
- If there is a sustained increase >25% stop the medication or seek advice from Nephrologist

SGLT2-inhibitors

Reduce renal tubular glucose reabsorption leading to glycosuria

Reduces glomerular hyperfiltration and slows the rate of progression of kidney disease

Have been demonstrated to reduce important kidney endpoints including ESRD

Need to apply for EDS

- Specific criteria for approval still requred

SGLT2-i EDS requirements

Unfortunately, in MB not covered by Pharmacare except under EDS part 3

- Need to have a history of cardiac, peripheral vascular or cerebrovascular disease
- Inadequate glycemic control despite metformin

SGLT2-i

If on insulin or sulfonylurea and HgbA1c <8.5% reduce dose by 20% before starting SGLT2i

If on diuretic, consider reducing diuretic dose with volume reassessment in 2 weeks

If on antihypertensives and BP <130/80, consider reducing dose with reassessment of BP in 2 weeks

Common side effects

Increased urination

Decrease blood pressure

Genital mycotic infections

Uncommon side effects

Diabetic ketoacidosis

Amputation/bone fraction (found in one study with canagliflozin)

Other interventions for diabetic nephropathy

Regular exercise program

Weight loss if obese

Smoking cessation

Low sodium diet

Avoid NSAIDS and other nephrotoxins

Target BP <130/80

Target HgbA1C <7%

Consider adding a statin

Assess other medications and adjust for eGFR

Non-diabetic kidney disease

Initial management of proteinuria

Depends on presentation and whether patient is asymptomatic vs symptomatic

- If symptomatic also need to treat the edema

Treatment of proteinuria

RAAS inhibition (ACE-I or ARB)

- If the renal function is much worse compared to baseline, this becomes a judgement call

Starting dose depends on blood pressure

- Consider stopping other antihypertensives if blood pressure is normal so that a RAAS inhibitor can be started

Titrate based on blood pressure

- Electrolytes, creatinine 1-2 weeks after starting

Treatment of proteinuria

Treat blood pressure to target

- <130/80 if possible
- Primary glomerulonephritis and young I will try to target <120/80

- Smoking cessation
- Weight loss
- Low salt diet

Initial management of nephrotic syndrome

Fluid restriction

- <2L per day, often <1.5L per day “all sources”

Salt restriction

- CKDpathway.ca under “medical management” has a good handout on sodium restriction

Avoid

These foods are high in sodium.

Salt, sea salt, or seasonings that contain salt

Hot cereals, instant, with added salt

Soup, packaged or canned

Packaged dinners

Processed lunch meat and frozen meats

Pickled products

Ham

Sausage

Bacon

Salted nuts or seeds

Processed cheese or cheese spreads

Hot dog

Salted chips, pretzels, or popcorn

Pizza

Pancakes or waffles, frozen or from mix

Soya, fish, or steak sauce and marinades

Packaged rice, noodle, and sauce mixes

Salt substitutes with potassium*

***Ask your dietitian or doctor if you can use salt substitutes.**

French fries, salted

Canned vegetables, salt added

Canned pasta sauce, tomato sauce, canned tomatoes with added salt

Tomato juice, vegetable cocktail

Initial management of nephrotic syndrome

Diuretics

- Usually need high doses to be effective
- Can start with furosemide 40 mg and titrate up to as much as 160 mg po BID
- Monitor electrolytes carefully until on a stable dose

Daily weights

- Same time each day, record weight
- Goal diuresis 1-2 lbs per day

Definitive management of proteinuria in GN

Need a renal biopsy to confirm diagnosis

Conservative management with RAAS-inhibitor vs immunosuppression depending on the diagnosis and patient

Trials starting to show benefit of SGLT2-i in non-diabetic kidney disease, but not yet standard of care

- IgA nephropathy (DAPA-CKD)
- EMPA-KIDNEY trial (results expected in 2022) enrolled patients with CKD **without** T2DM

Please refer

Refer earlier rather than later

Patients with a possible GN need to be seen and biopsied

Nephrology probably doesn't add much to the treatment of diabetic nephropathy at earlier stages, but patients with significant proteinuria are at high risk to progress and require education/CKD complication management

Questions?